This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's

January 11, 1996

To Whom It May Concern:

The Food and Drug Administration (FDA) is aware that your company may be interested in the opportunity to manufacture, distribute and/or market silicone gel-filled breast implants. The purpose of this letter is to inform you of the clinical data needed to submit a Premarket Approval Application (PMA).

The FDA requests that each company conduct a prospective "Core" clinical study (preceded by a small Pilot study) to assess the safety and effectiveness of their silicone breast implants. In an effort to facilitate your possible submission and FDA review, we have developed preliminary guidance for the design of the Core study protocol.

The Agency also expects applicants to provide retrospective data on the frequency and consequences of implant ruptures. This may be obtained through study of previously marketed implants, or by relating available data to the proposed product through appropriate in vito testing. Guidance for the design of this retrospective rupture study will be outlined in a subsequent letter.

FDA suggests that a Pilot study be conducted before the Core study protocol is finalized. We suggest it include at least 30 augmentation patients and 30 reconstruction patients. Advantages of performing such a Pilot study include: 1) an opportunity to validate specific study design/documentation details; 2) the estimation of short-term adverse event rate for your product to determine the specific sample size needed for the Core study; and 3) an opportunity to gain initial human experience with the final product. We encourage you to meet with FDA to discuss details of the pilot study design for your product.

The Agency anticipates the **Core** study will include:

- Sufficient numbers of women to determine the rupture rate with reasonable precision, we suggest 500 women to be followed to the end of

the study. Estimating a 40% drop out rate, we recommend recruitment of at least 850 subjects. This will provide precision of +/- 4% at a rupture rate of 50% and +/- 1.9% at a rupture rate of 5%.

- Separate tracking and evaluation of reconstruction patients (300-350) and augmentation patients (500-550) is recommended.

- The Core study should include 18 month experience with 650-700 patients (including at least 25% reconstruction patients) prior to submission of the PMA, and two year experience prior to PMA approval. There should be at least 10 years of follow-up including both premarket and postmarket evaluations. The initial consent form should reflect the total length of the study follow-up.

- Determination of infection, contracture, failure rates and other safety evaluations should occur periodically. We suggest collecting data at three months, six months, one year, 18 months and two years. After the two year follow-up, annual patient evaluations are recommended.

- To support approval, we feel the Core study should determine the incidence, timing and clinical consequences of silent rupture. This could be accomplished through sequential screening of a subgroup of the study population using MRI or other imaging techniques.

- Quality of Life assessments in a subset of the study population might be beneficial and should be considered.

- A Connective Tissue Disease (CTD) screening questionnaire should be conducted after patient enrollment, but before implantation, and again during follow-up visits. Symptoms should be followed over time, with referral to a rheumatologist if appropriate, for diagnosis and treatment. This screening questionnaire will be used to document patients' pre-implantation CTD status and identify any patients who develop CTDs.

- Determination of gel bleed potential may be made by pre-clinical assessment.

This represents our current thinking on the study design for silicone gel-filled breast implants. We welcome feedback or alternative suggestions. We recognize that testing may be tailored to the specific product, and encourage you to meet with FDA before finalizing a study protocol.

We are currently developing a more complete guidance document to aid manufacturers with the testing and submission of silicone, saline, and alternative breast implants. We hope to have this guidance available later this year.

I hope the information above will help you design and submit an effective protocol for assessment of silicone gel-filled breast implants. If you have any questions, please call Ms. Beth Nairn, Breast Implant Coordinator at (301) 594-3090.

Sincerely yours,

/S/

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